Interaction between CNS-resident cells and gut dysbiosis in multiple sclerosis

Consequences on neuroinflammation

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Introduction

Neuroinflammation is a hallmark of multiple sclerosis (MS), in which microglia and astrocytes are key players. Given the multifactorial etiology, gut dysbiosis has emerged as a potential pathogenic factor. Despite being extensively studied how microbial immunomodulatory metabolites impact on T-lymphocytes, less is known about the effects on microglial and astrocytic activity and the consequences on neuroinflammation.

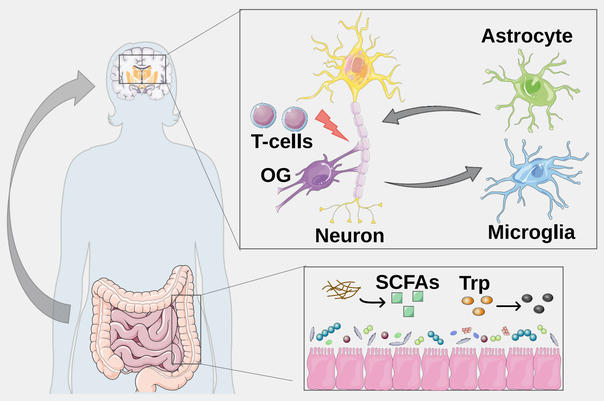

Figure 1. Diagram of MS pathogenesis. *OG: Oligodendrocyte; SCFAs: Short-chain fatty acids; Trp: Tryptophan.*

Aims

- To describe the profile of gut microbiota in patients with MS.
- To determine the role of CNS-intrinsic cells (microglia and astrocytes) in MS pathogenesis.
- To analyse the interaction between microbiome and CNS-resident cells, emphasising in dietary tryptophan metabolites and short-fatty chain acids.
- To study its consequences in regards to the neuroinflammation present in MS.

Methodology

- Search on Pubmed database.
- Keywords (alone or in combination): “microbiota”, “dysbiosis”, “multiple sclerosis”, “microglia”, “astrocytes”, “tryptophan metabolites”, “SCFAs”.
- Selection criteria: Journal impact factor, date of publication (last 5 years) and relation with the review topic.
- Reading and summary of the selected articles; exhaustive analysis of their bibliography.

Gut dysbiosis in MS patients

Dysbiosis in MS patients has been constantly observed in several studies, with subtle changes in the relative abundance of some specific bacterial genera.

A generalized “MS microbiota phenotype” has not been described, suggesting that many factors can influence its composition (e.g. age, diet, geographical features).

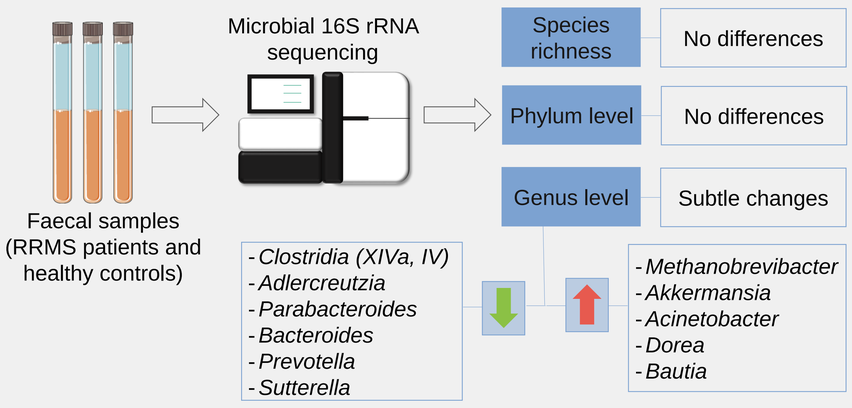

Figure 2. Profile of gut microbiota in MS patients. The diagram summarizes the changes identified in 4 studies (*Jangi S et al (2016), Chen J et al (2016), Miyake S et al (2015)* and *Cekanaviciute E et al (2017)*). *rRNA: ribosomal RNA; RRMS: Relapse-remitting multiple sclerosis.*

Microglia and astrocytes in the pathogenesis of MS

Whereas in the disease onset neuroprotective M2 microglia and A2 astrocytes promote axonal regeneration and remyelination, their neurotoxic and demyelinating properties predominate to the extent that the disease progresses due to a shift to proinflammatory M1 microglia and reactive A1 astrocytes.

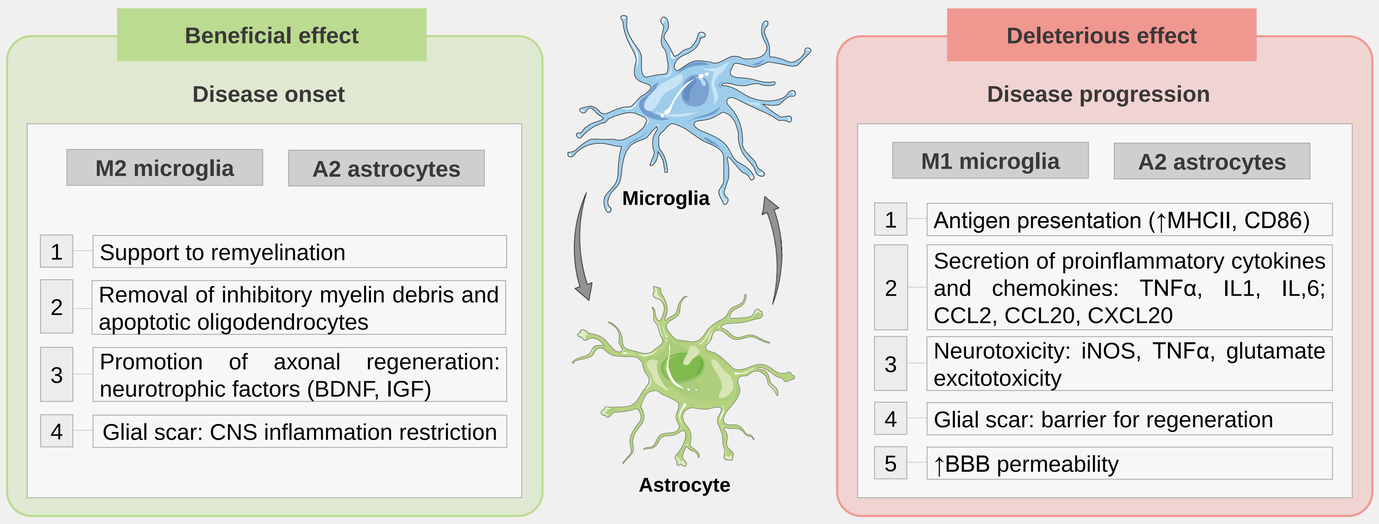

Figure 3. Dual role of microglia and astrocytes in MS. CNS-resident cells, mainly microglia and astrocytes, are key players in neuroinflammation. They have a dual role in MS, being their activity favourable or damaging, depending on the stage of the disease.
BDNF: Brain-derived neurotrophic factor; IGF: Insulin growth factor; MHCII: Major histocompatibility complex II; TNFα: Tumor necrosis factor alpha; CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; IL: interleukin: iNOS: inducible nitric oxide synthase; BBB: Brain-blood barrier

Modulation of neuroinflammation by microbiome in MS

Dietary tryptophan metabolites

Dietary tryptophan metabolites (indoles and other derivatives) act as aryl hydrocarbon receptor (AHR) ligands. In MS patients, circulating levels of AHR agonists are lower in comparison with control individuals. As a consequence, their capability to reduce the proinflammatory phenotype of microglia and astrocytes is impaired and neuroinflammation and MS are worsened.

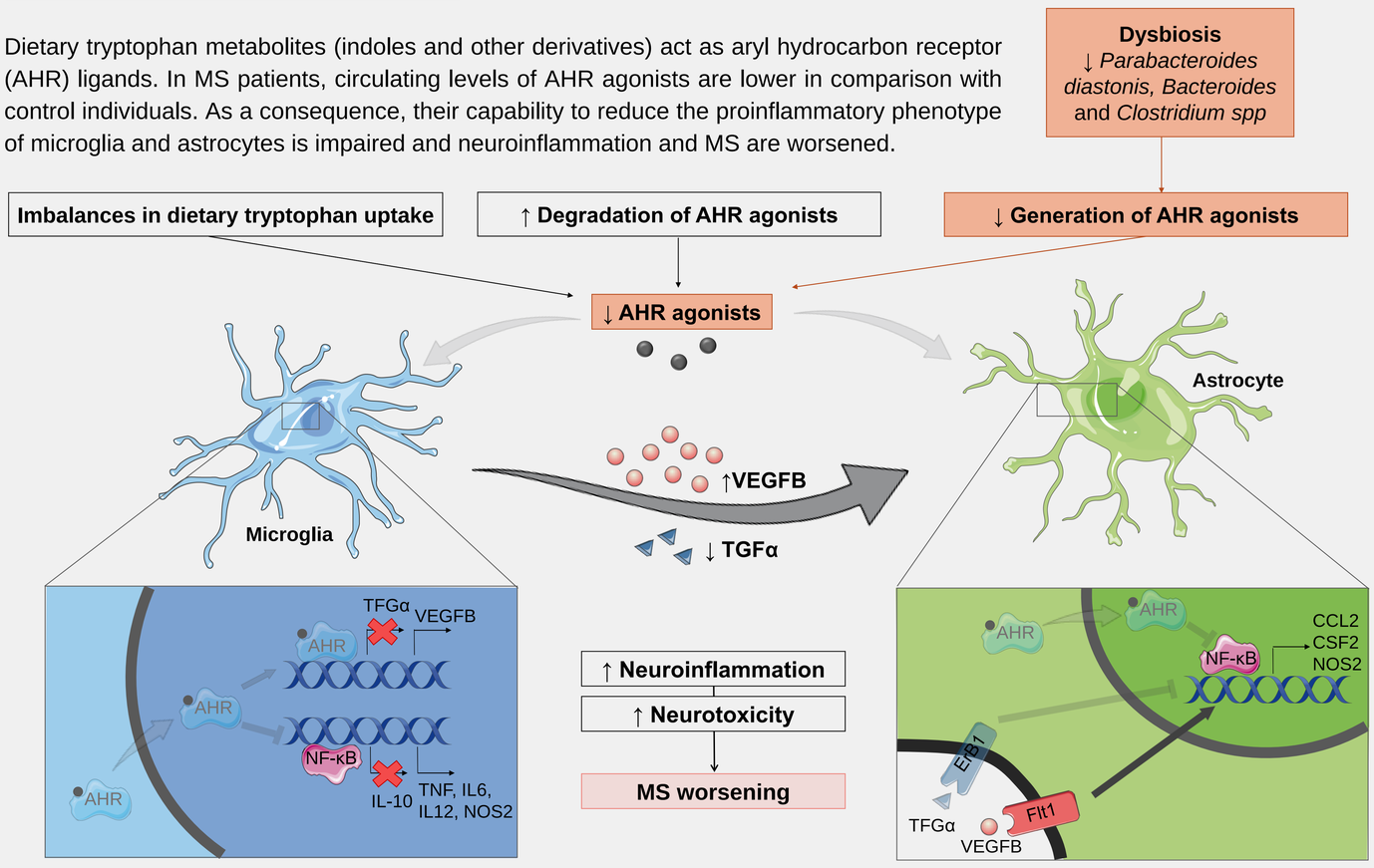

Figure 4. Enhancement of neuroinflammation in MS due to low tryptophan metabolites levels, promoting the secretion of proinflammatory cytokines, chemokines and neurotoxic factors from astrocytes and microglia directly and also indirectly, through the modulation of the ratio VEGFB/TFGα in microglia. *TGFα: Transforming growth factor alpha; VEGFB: Vascular endothelial growth factor B; Flt1: Fms related tyrosine kinase 1; NF-κB: Nuclear factor kappa b; CSF: Colony-stimulating factor.*

Short-chain fatty acids

Short-chain fatty acids (SCFAs) are immunomodulatory metabolites. In MS patients, circulating levels of SCFAs are decreased as a consequence of the dysbiosis. SCFAs are important in the modulation of microglia maturation and function; however, little is known about the consequences on neuroinflammation in MS.

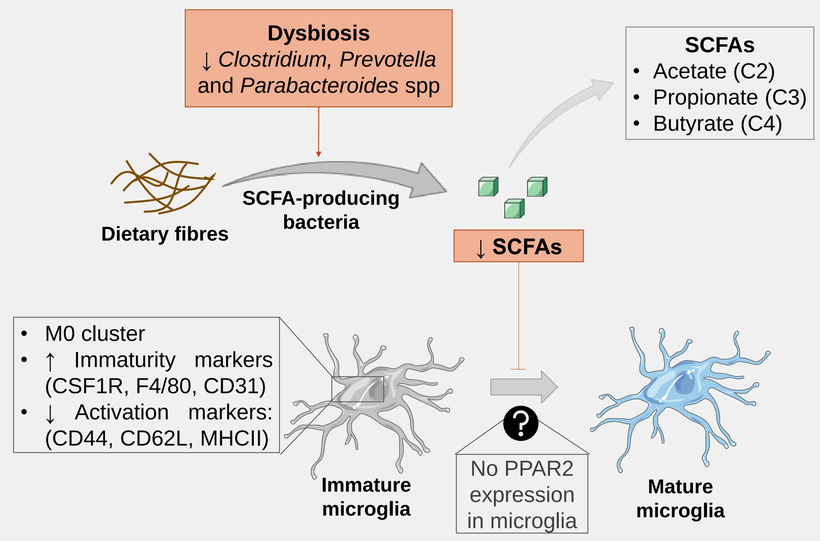

Figure 5. Alteration of microglia maturation owing to SCFAs levels’ reduction, even though the consequences on MS progression have not been described.
CSFR: Colony stimulating factor receptor; PPAR: Peroxisome proliferator-activated receptor

Conclusions

- Gut dysbiosis may predispose or modify the course of MS.
- The functional relevance of the interaction between CNS-resident cells and microbiome in MS pathogenesis remains unknown.
- Given the pathogenic role of microglia and astrocytes, determining the specific mechanisms by which gut microbiota, astrocytes and microglia interact may be relevant to develop new therapeutic approaches.
- Most studies have used EAE model or RRMS patients. Studies of gut microbiota in patients with progressive MS may reveal possible other changes in microbial populations.
- It can be extrapolated to other neurodegenerative disease where a dysbiosis has been identified (e.g. Parkinson or Alzheimer diseases).

References

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